Sensory feedback signal derivation from afferent neurons

Contract No.: **NIH-NINDS-NO1-NS-3-2380**

QUARTERLY PROGRESS REPORT #2

for the period

1 March 1992 -- 31 May 1993

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Date of submission of this report: 13 July 1993

I. Summary of the Overall Project

In this study we are exploring the feasibility of extracting 1) cutaneous sensory information about fingertip contact and slip, and 2) proprioceptive sensory information about wrist or finger position. We use implanted nerve cuff electrodes to record peripheral nerve activity in animal models.

Our overall **objectives** for the 3-year duration of this contract are as follows:

1. Investigate, in cadaver material, implantation sites for nerve cuff electrodes from which cutaneous and proprioceptive information relevant to the human fingers, hand and forearm could be recorded.

2. Select a suitable animal preparation in which human nerve dimensions and electrode placement sites can be modeled and tested, with eventual human prosthetic applications in mind.

3. Fabricate nerve cuff electrodes suitable for these purposes, and subcontract the fabrication of nerve cuff electrodes of an alternate design.

4. Investigate the extraction of information about contact and slip from chronically recorded nerve activity using these animal models and electrodes. Specifically,

   a. Devise recording, processing and detection methods to detect contact and slip from recorded neural activity in a restrained animal;

   b. Modify these methods as needed to function in an unrestrained animal and in the presence of functional electrical stimulation (FES);

   c. Record activity for periods of at least 6 months and track changes in neural responses over this time.

5. Supply material for histopathological examination from cuffed nerves and contralateral controls, from chronically implanted animals.

6. Investigate the possibility of extracting information about muscle force and limb position from chronically recorded neural activity.

7. Cooperate with other investigators of the Neural Prosthesis Program by collaboration and sharing of experimental findings.

II. Summary of Progress Prior to the Second Quarter

In the first quarter we completed objective 1 and made progress toward objectives 2 and 3. In three human cadaver arms, we found appropriate implantation sites for nerve cuff electrodes from which cutaneous and proprioceptive information relevant to the human fingers, hand and forearm could be recorded. We selected the cat forelimb as the animal preparation in which human nerve dimensions and electrode placement sites are being modeled and tested. We investigated the details of the innervation of the paw and the forelimb musculature in three cats, identified several possible implantation sites, and started to design cuff electrodes suitable for these purposes.

III. Summary of Progress in the Second Quarter

Activities: In the second quarter we built 38 nerve cuff electrodes in assorted sizes (Table 1), suitable for implantation on four nerves in the left forelimb of cats: the proximal median nerve, proximal ulnar nerve, distal median nerve, and distal ulnar nerve (objective 3). We implanted four cuffs in each of three cats, and began to follow the cuff impedance and compound action potential (CAP) properties periodically to determine long-term viability (objective 4c). We also started to design a forelimb reaching task and the hardware required to extract information about contact and slip from chronically recorded nerve activity (objective 4a,b).

Personnel: The list of co-investigators in the cover page of this report reflects the growth in the number of students who joined my laboratory and are now participating in this project. K. Strange is an engineer who enrolled in the MASc program in Engineering Science at SFU. In March and April of 1993 he worked 100% of his time in this project; since May 1 he is working 60% time. S. Schindler is a physical therapist who enrolled in the MSc program in Kinesiology on May 1, and is working 60% time on this project. I. Valenzuela is an engineer who is working 100% time during the summer. None of these co-investigators is being paid from this NIH contract, but is it appropriate to acknowledge that their time and effort is being directed in support of this project.

IV. Progress in the Second Quarter

A. Design of Nerve Cuff Electrodes

General considerations: Nerve cuff recording electrodes consist of an insulating cuff (e.g., silicone tubing) that contains several circumferential metal electrodes (e.g., multistranded, flexible stainless steel wire, Teflon-coated), placed around a length of peripheral nerve. The design, fabrication and surgical installation of nerve cuff recording electrodes were reviewed in detail by Hoffer (1990). The insulating cuff serves to resolve the small action currents generated by nerve fibers, by constraining the current flow within a long, narrow resistive path. The insulating cuff also reduces the pickup of electromyographic (EMG) potentials generated by nearby muscles as well as signals generated by any other sources outside the cuff. Rejection of unwanted signals is optimized if differential recording from a 'balanced tripolar' electrode configuration is used (Hoffer, 1975; Stein et al., 1975, 1977). Four main parameters, fiber diameter, cuff inside diameter, cuff length, and interelectrode distance, determine the shapes and amplitudes of the axonal potentials recorded (Marks and Loeb, 1976). To obtain maximal signal amplitudes, the length of a nerve cuff should be close to the wavelength of neural action potentials (30-40 mm), and about 10 times greater than the I.D. The aggregate electroneurographic (ENG) activity recorded from a nerve depends on the number of active fibers, is usually dominated by the activity of the largest axons, and is biased in favor of superficial axons; in 1-4 mm diameter nerves, action potential amplitudes recorded from deep axons can be attenuated 2- or 3-fold (Marks and Loeb, 1976; Stein and Oguztöreli, 1978; Hoffer et al., 1981a). Cuff impedances usually range between 2 and 20 kΩ, using a 1 kHz sinusoidal test signal. ENG amplitudes recorded during walking have ranged from about 5 μV (peak-to-peak) for the cat sciatic nerve (using a 4 mm I.D., 30-mm long cuff), to up to 90 μV (peak-to-peak) for the much finer rabbit tenuissimus nerve (using a 0.3 mm I.D., 5-mm long cuff). Since the nerve cuff source impedance is low and the signal amplitude is small, an ultra-low noise, low input impedance differential preamplifiers are used (e.g., Leaf Electronics QT- 5B; Charles, 1989).

B. Construction of Tripolar Nerve Cuff Electrodes

1 Select appropriate tubing. We use silicone tubing stock in standard sizes provided by either Dow Corning or Sil-Med Corp. In the second quarter, we built the following 38 cuffs intended for the cat median or ulnar nerves at locations above and below the elbow:

Table 1: Cuff inventory and coding

Internal Diameter (mm)	Length (mm)				
	5	10	15	17.5	20
1.0	1	1	1	1	1
1.6	1	2	2	1	1
2.0	1	1	2	1	1
2.5	1	2	4	0	1
2.8	1	2	1	0	1
3.4	1	2	3	0	1

2 Cut tubing. The tubing is cut cleanly with a sharp scalpel or razor blade. The length of the cut piece should be exactly the desired length of the finished cuff. Simply pressing down on the tubing with the blade will distort the tubing and will not result in a straight cut. Cutting back and forth while pressing down results in a straight cut provided the blade is allowed to cut and not pushed so much that it deforms the tubing. Inserting a piece of plastic, wood, or Teflon tubing inside the silicone tubing and then placing the blade on top and rolling the whole assembly also results in a clean, straight cut. With this method, care must be taken that the blade is oriented perpendicular to the longitudinal axis of the tubing or a spiral cut will result.

3 Prepare Cooner wires. Without cutting the wire, pull about 70 cm of AS-631 Cooner wire off the spool and strip 3 cm of Teflon off the end using light pressure on #5 Dumont forceps. It is easier to accomplish this 1 cm at a time instead of all at once. Be careful not to nick the stainless steel strands inside. If in doubt, check the removed insulation under the microscope for any cut strands. Alternatively, a DC current heated tungsten loop can be used to vapourize the Teflon locally.

The strands should be twisted such that the bundle acts as one wire instead of 9 independent strands. To do this, hold de-insulated end and twist insulated part between thumb and forefinger. Note that the ensuing twist in the Teflon coated wire portion will have to be released or kinks will result.

4 Micro weld tungsten needles to Cooner wire. Without cutting the tungsten wire, pull enough off the spool to reach the micro welder. Place the Cooner wire tip over a 0.005" tungsten wire at an angle not greater than 30° and weld together (125 v, 2.2 oz.). This is easiest if the Cooner wire overlaps the tungsten wire by approximately 3 mm. Test to ensure that all strands are welded by moving joint around while viewing through the microscope. Fold the Cooner wire ends back along the Cooner wire. It should be possible to run pressed thumb and forefinger along the tungsten wire onto the stainless without dislodging any strands. After determining the integrity of the weld, cut the tungsten wire to length 1.5 times the outer diameter of the silicone tubing with the heavier duty wire cutters. Now, measuring from the beginning of the insulation, cut the Cooner wire to 70 cm.

5 Thread electrodes through tubing. Using the tungsten wire held by forceps as a needle, poke a hole (hole 1) in the near wall and out (hole 2) the far wall of the silicone tubing and thread the de insulated portion of the Cooner wire through it. Pull the wire through until the remaining insulation abuts onto the silicone. Note that it must exit the other side adjacent to, but not on, the center line. Then the wire must be anchored there by poking and threading back through the wall of the tubing into the lumen via a different hole (hole 3.). Hole 3 must be no closer than 0.5 mm from hole 2 or the wire will cut the silicone. With the tungsten needle, wrap the distal end of the wire around the proximal part of the wire several times before exiting the tubing near hole 1 (hole 4). Do not pull all the slack through. Instead, pull only enough slack through such that the two wires course along the inner surface of the tubing. Press the wires against the inner surface of the silicone tubing with a glass tube or similar rounded instrument.

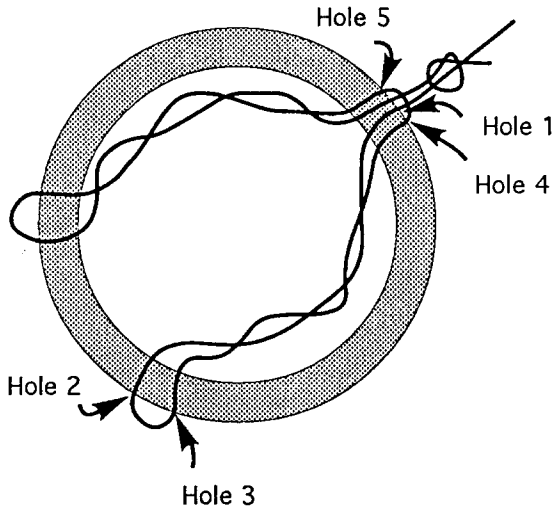

Figure 1: Wire course through cuff walls

Poke hole 5 near hole 1 (not less than 0.5 mm apart) and repeat the above process on the other side of the centre line. After exiting from hole 8, the remaining de insulated wire is tied (overhand knot) around the insulated Cooner wire at its silicone tube entry point. To align holes along the length of the tube, draw a centre line with an acetone-soluble marking pen, use the light reflection line off the surface of the silicone tubing, a steel rod inside the tube, or the silicone tubing can be placed lengthwise under the microscope and the holes aligned by sighting down the length of the tubing. Using any of these techniques, it should be possible to put the required number of electrodes in the tubing and have them all line up.

The middle electrodes must be further from the centre line than the edge electrodes (see below) to prevent shunting via the centre gap (the silicone flap also helps). The outer electrodes should be placed 1 mm from the outside edge of the cuff. The centre electrode should be equidistant from the two outer electrodes not the outside edge of the cuff .

6 Make the cut along the offset cut line in one motion (to avoid jagged edges) by pressing down on a sharp razor blade against a non-metallic rod inserted in the lumen. Note that the cut is made adjacent to, not on the centre line. This is so that the silicone flap can lay flat against the silicone tube and not above the anchor point silicone bead (which would prohibit a tight seal). Be careful not to make the cut any closer than 0.5 mm to the electrode anchor points.

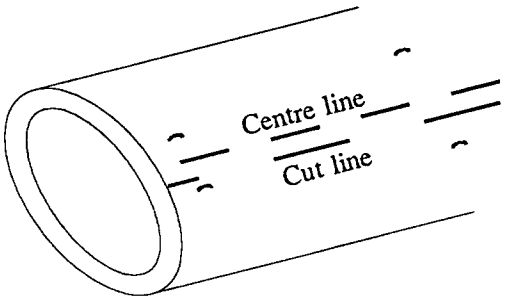

Figure 2: Anchor point location and cut reference lines

7 **Insulate the wire anchor points** with silicone adhesive. Ensure that the entire anchor is covered and that the junction of the Teflon coated wire and the cuff is well insulated. At the same time that the anchors are being insulated, Dow-Corning 500-1 (L = cuff length, W = 1.5 to 2.0 mm) silicone flap can be glued in place. Try to avoid a large buildup of silicone on the anchors on the non-attached side of the flap so the flap can lay as flat as possible. Keep silicone away from the cut edge. A small amount here can prevent the gap from closing upon installation or could glue it closed. Cure in oven at 60 °C.

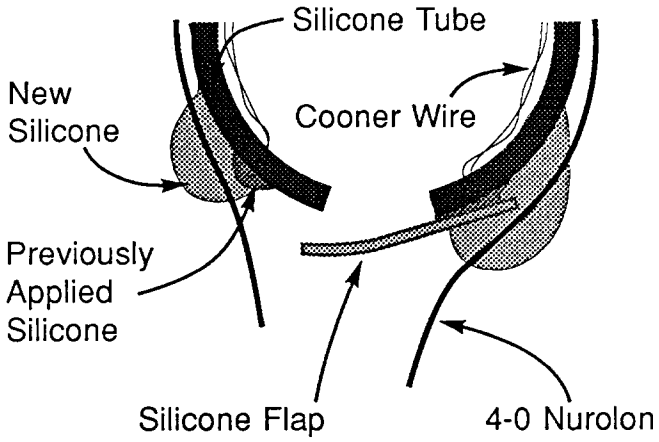

Figure 3: Silicone flap, anchor point, and suture detail

8 **Place sutures** (4-0 Nurolon) around the cuff and secure in place with silicone. To do this, place stage 8 cuff on Pasteur pipette longitudinally mounted on an aluminum plate edge and attach 15 cm long sutures spaced 5 to 6 mm longitudinally along the cuff. The suture material should be longer on one side than on the other (60/40) for ease of use in surgery. Anchor the sutures with generous quantities of silicone, especially near the cut since they will be subject to the most tension. Cure in oven at 60 °C. Next, tie the three sutures on either side in an overhand knot such that equal tension is placed on each of the threads.

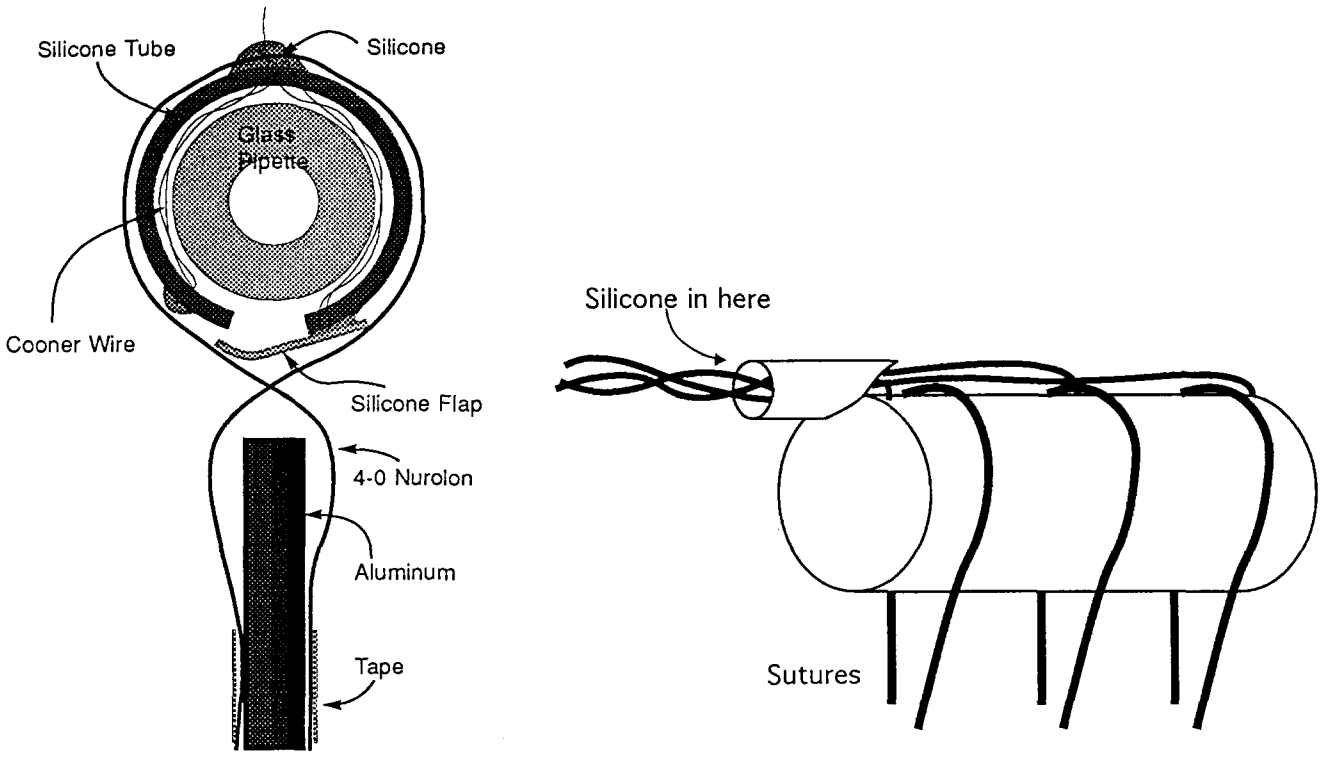

Figure 4: Suture attachment method and strain relief detail

9 Attach strain relief tubing (bevel cut Dow-Corning 602-135 tubing 6-8 mm long) and fill with silicone. Ensure that all leads are exactly the same original length so that when the leads are arranged parallel to the cuff, they are coded by length (i.e., the longest lead is the proximal electrode). Form a wire "rope" by twisting all three strands in the same direction simultaneously and allowing the natural winding to occur. Tie ends to prevent unraveling and code with colour beads.

10 Clean the finished cuff ultrasonicating in warm soapy tap water (10 minutes) followed by a distilled water rinse (5 minutes). Ultrasonicate for 10 minutes in acetone and let dry.

11 Quality Control. Check the following features of the cuff:

- anchor points and wire-cuff junctions well insulated?
- electrodes snug against inner surface of cuff tubing?
- electrodes not splayed in cross sectional plane?
- electrical connection to end of lead wires?
- wire length coding obvious and correct?
- nerve cuff clean?
- sutures of graspable length on both sides of cuff?
- suture knot equalizes tension on all leads?
- cuff closes well (no silicone in opening)?

12 Wind the lead out wires loosely into a coil. Package the cuff in an autoclave envelope with all pertinent cuff specifications written clearly on the back.

C. Compound Action Potential Recording Protocol

1 Record Tripolar Cuff Impedances

The impedances of the four tripolar cuffs are recorded using an impedance meter (Bak Electronics, Model IMP-1) periodically over the duration of the chronic studies. The impedances affect the stimulation currents required to recruit nerve fibers, as well as the amplitude of the neural signals recorded with the cuff electrodes (viz., Stein et al., 1978).

2 Stimulation Waveform

A biphasic charge-balanced waveform is generated with a pulse generator (Bak Electronics Inc., Model BPG-2) controlling a constant current stimulator (developed in-house). The first pulse is negative with the amplitude determined by the constant current generator and the duration determined by the biphasic pulse generator (50 ms). The second pulse is positive and is one-tenth the amplitude and ten times the duration of the negative pulse to ensure charge balancing. The waveform is applied to the centre electrode of the tripolar stimulation cuff using the electrode furthest from the recording cuff as the reference. The typical stimulus repetition rate is 1 Hz.

3 Recording Instrumentation

Tripolar nerve cuff signals are measured on the centre electrode of the recording cuff with reference to the two outside electrodes in parallel. The signals are amplified (typically by 10^4 - 10^5) using low-noise preamplifiers (Leaf Electronics Ltd., Model QT-5A) and amplifiers (Bak Electronics Inc., Model MDA-1) to a level such that signals are detectable on the oscilloscope and do not exceed 4 V p-p, so as not to be clipped when recorded on FM tape. A 20 channel FM tape recorder (Honeywell, Model 96; 0-10 KHz) is used to record all of the nerve cuff signals, as well as an EMG signal from implanted electrodes in the Palmaris Longus muscle, a stimulus synchronization signal, a stimulus intensity signal, and a time code signal (Datum Time Code Generator, Model 9300).

4 Recording Protocol for Median Nerve

a Stimulate Distal Cuff, Record from Proximal Cuff

The stimulation threshold of the distal median nerve is determined by increasing the stimulation intensity until a small compound action potential (CAP) is detected from the proximal cuff. The supramaximal stimulation intensity is determined by increasing the intensity to a level such that all large fibers in the median nerve surrounded by the stimulation cuff are recruited. The CAP recorded from the proximal cuff is shown in Fig. 5A. Figures 5 and 6 show data obtained from the second cat implanted in this series.

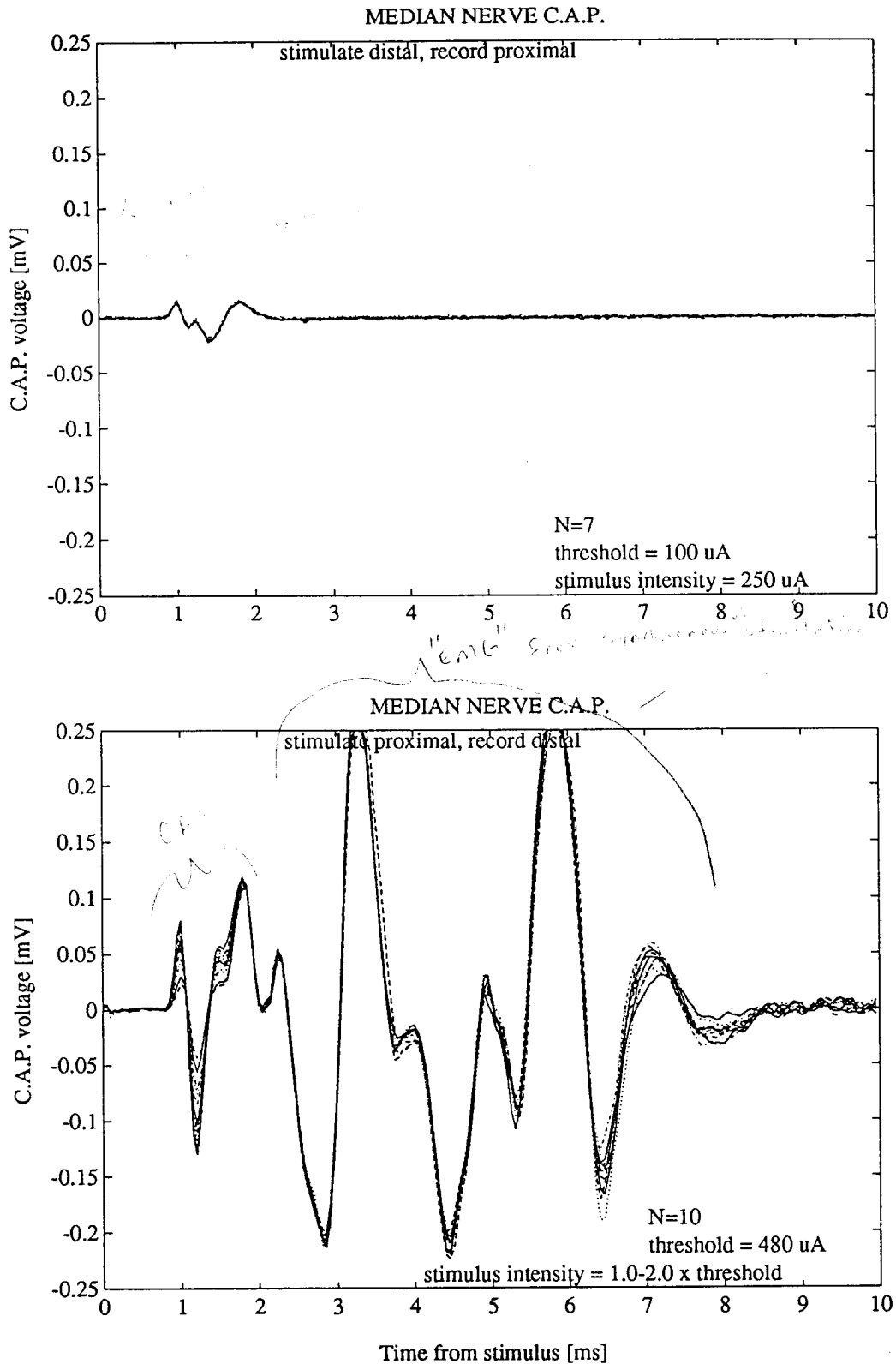

Figure 5: Median Nerve CAPs.
A: stimulate distal, record proximal. B: stimulate proximal, record distal.

In Fig. 5A, the CAP shows the classic positive-negative-positive waveform resulting from a tripolar cuff. Quite often two or more sets of fibres are recruited that display distinct conduction velocities so the CAP can become somewhat distorted as peaks of different CAPs have positive and negative interference as shown in Fig. 5A. At supramaximal stimulation, the times to CAP onset, first positive peak, and first negative peak, as well as the peak amplitudes are recorded. In the case of multiple negative peaks, the largest negative peak data is recorded. The temperature in the limb is recorded by using an implanted thermistor (Yellow Springs Instrument Inc., Model 44004, embedded in silicone). Rectal temperature is also recorded.

At least 25 stimulations of the supramaximal CAP are recorded on FM tape for later analysis. The amplifiers used for that channel are calibrated so that the actual signal amplitudes can be determined.

b Stimulate Proximal Cuff, Record from Distal Cuff

This recording is basically the same as the previous recording on the median nerve except that stimulating the proximal cuff recruits motoneurons that innervate muscles below the elbow resulting in generation of EMG that is picked up by the distal recording cuff. Figure 5B shows the CAP which begins just before 1 ms and the EMG signal that begins after the CAP. The EMG signal usually starts at longer latency than the CAP but it may distort the second positive peak of the CAP or even the negative peak, depending on the exact cuff location below the elbow and its distance to the muscles surrounding it, and the relative conduction velocities of median nerve axons located inside and outside the distal cuff. The times and amplitudes of maximum positive and negative peak values of the EMG pickup signal are also recorded. Changes in the EMG pickup amplitude and in the ENG:EMG signal-to-noise ratio over the duration of the chronic experiment give an indication of changes in EMG rejection and its possible causes, e.g., opening of the cuff and connective tissue invasion.

The EMG pickup in the distal ulnar cuff is also recorded during median nerve stimulation, to monitor the EMG pickup/rejection properties in a cuff placed on a non-stimulated nerve.

5 Recording Protocol for Ulnar Nerve

This recording protocol replicates the protocol for the median nerve concerning stimulation intensities, the measurement of times and amplitudes of the CAP, and the EMG signal parameters on both the distal ulnar and distal median cuffs. An example of the ulnar nerve CAP recorded from the proximal cuff is shown in Fig. 6A. An example of the ulnar nerve CAP recorded from the distal cuff is shown in Fig. 6B.

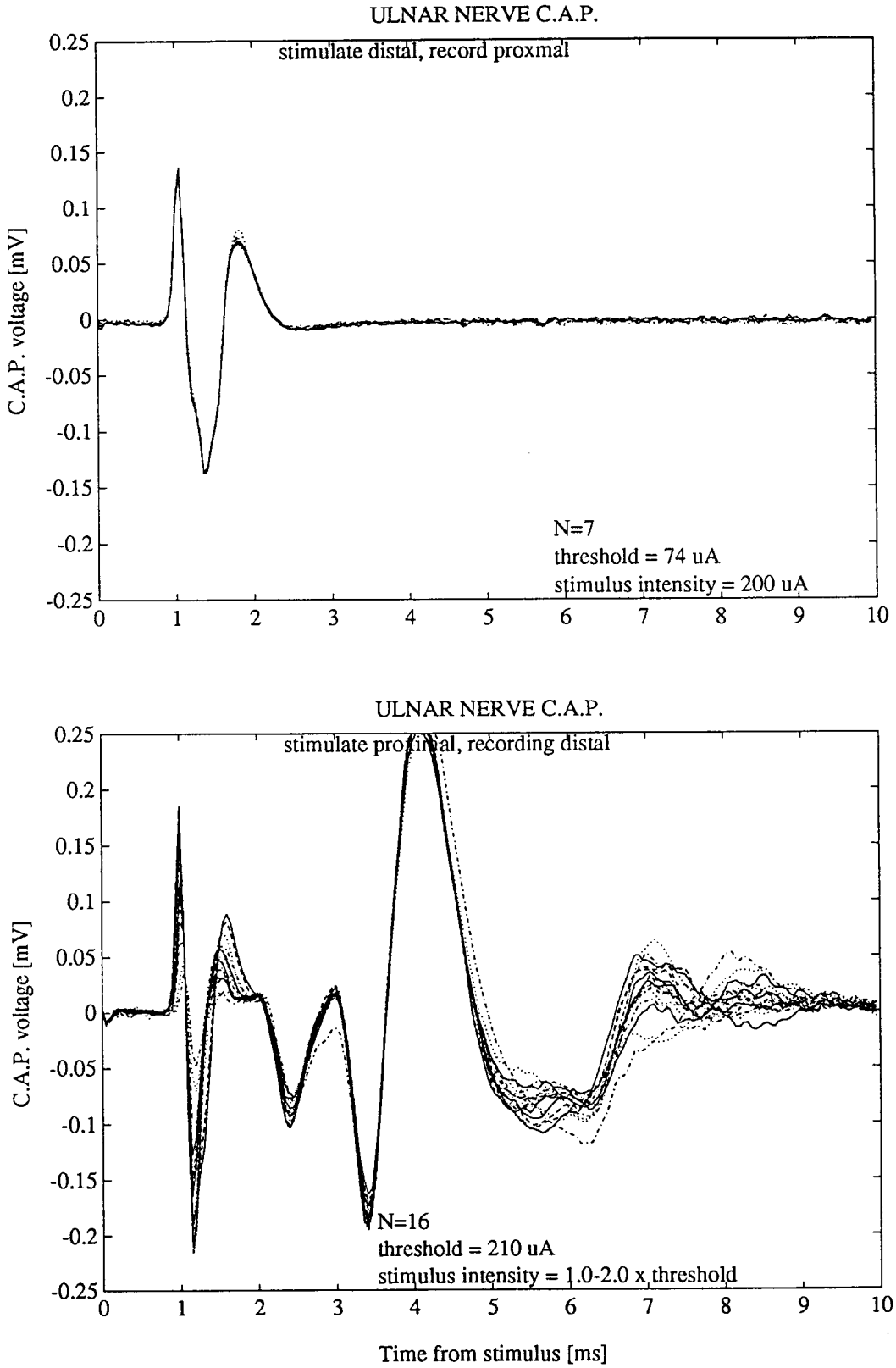

Figure 6: Ulnar Nerve CAPs.
A: stimulate distal, record proximal. B: stimulate proximal, record distal.

Note that the ulnar CAPs are of larger amplitude than the corresponding median nerve CAPs (shown in Fig 5A, B), which agrees with the differences in cuff dimensions and impedances found for these nerves (Fig. 4).

6 Exploration of Receptor Fields

The receptor fields of both the ulnar and median nerves are determined by studying the afferent activity picked up in the distal and proximal cuffs resulting from limb movements and mechanical stimulation of the mechanoreceptors in the glabrous skin in the paw. The raw signals are fed into a Paynter Filter (Bak Electronics Inc., Model PF-1) which produces a rectified envelope of the input signal. Both the raw cuff signal and the envelope are displayed on an oscilloscope. The frequencies of the afferent signals occur in the auditory range and an amplifier and speaker are used to provide auditory monitoring of afferent activity. The receptor fields are routinely examined following surgery to determine that nerve identification and cuff implantation during surgery were correct and the nerves remained viable distal to the distal cuffs.

D. Preliminary Results

1 Cuff Impedances

Cuff impedances recorded using a 1kHz signal measure mainly the resistance of tissue and fluid within the cuff. Initially the nerve occupies 70-80% of the cuff volume and the rest is filled by fluid. As connective tissue replaces this fluid over the next few weeks, the cuff impedance can be expected to rise (Stein et al, 1978). Indeed, during the first month after implantation the cuff impedances tended to increase systematically. This trend is shown in Fig. 7 for the 4 cuffs implanted in the third cat in this series.

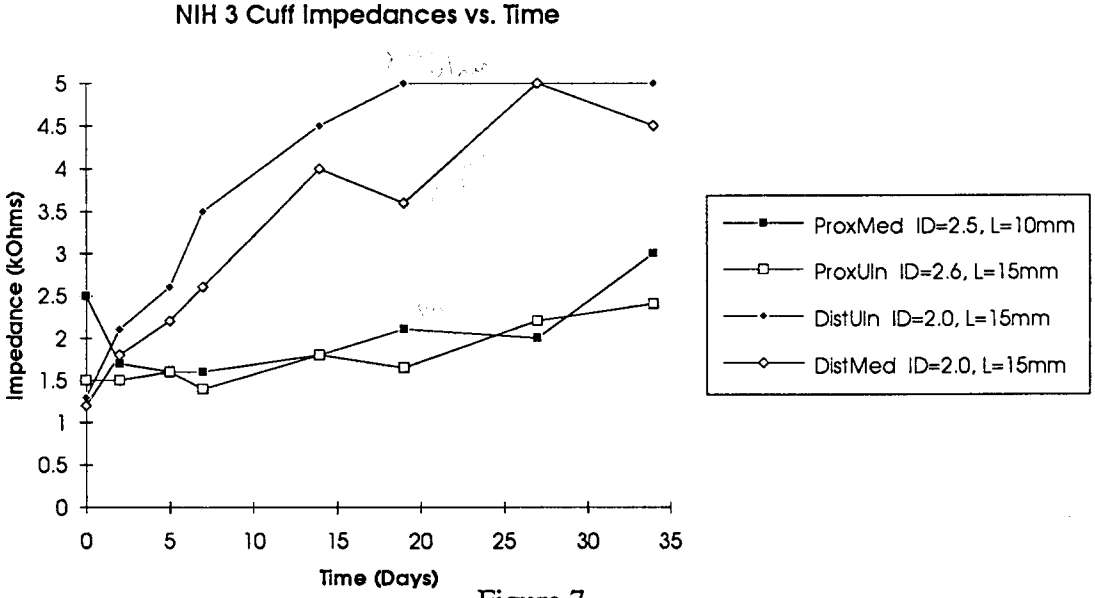

Figure 7

2 Time to Nerve CAP Onset

The time of onset of the nerve CAP should correlate with the fiber size recruited. Using our stimulus parameters, as the stimulation current increases, smaller, slower fibers will be recruited. If there is no injury to the population of large-diameter neurons, no change should be expected in the time of the onset at supramaximal stimulation. However, limb temperature has a significant effect on nerve conduction velocity. Our findings so far (e.g., Fig. 8) do not indicate significant changes in the onset time unrelated to temperature fluctuations.

Figures 7, 8, 9 and 10 show data obtained from the third cat implanted in this series.

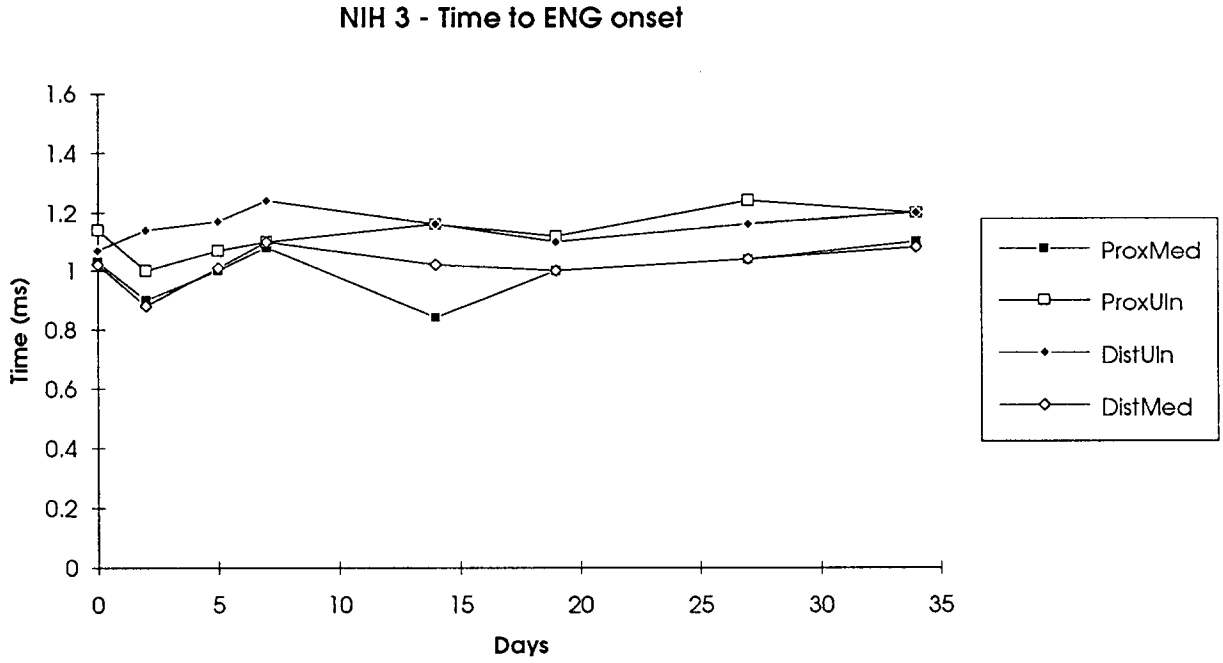

Figure 8

3 Amplitude of Nerve CAP

The peak-to-peak amplitude of the CAP is proportional to the aggregate nerve activity recruited inside the cuff (Davis et al., 1978). If the nerve has been traumatized by the surgery or by subsequent movement of the cuff, the amplitude is expected to decrease rapidly (Stein et al., 1979). In case of a non-traumatic implantation, the peak-to-peak values can be expected to increase somewhat as connective tissue fills the cuff, as seen for the data from Cat 3 (Fig. 9).

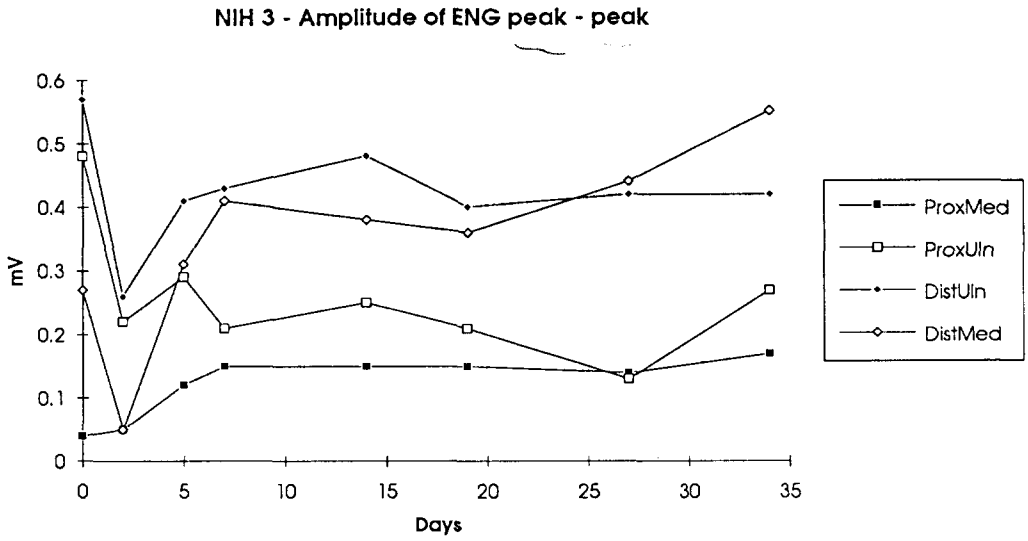

Figure 9

4 Amplitude of EMG Pickup

The peak-to-peak amplitude of the EMG CAP signal reflects the EMG rejection efficiency of the cuff. If connective tissue grows through the opening of the cuff, a significant increase in the EMG pickup can be expected. After the initial 1-2 weeks we have found stable EMG amplitudes. The EMG picked up by the cuff on the nerve being stimulated is significantly larger than the pickup by the cuff on the alternate nerve. This is likely due to the anatomical location of the cuffs and the rapid decline of EMG signals with radial distance.

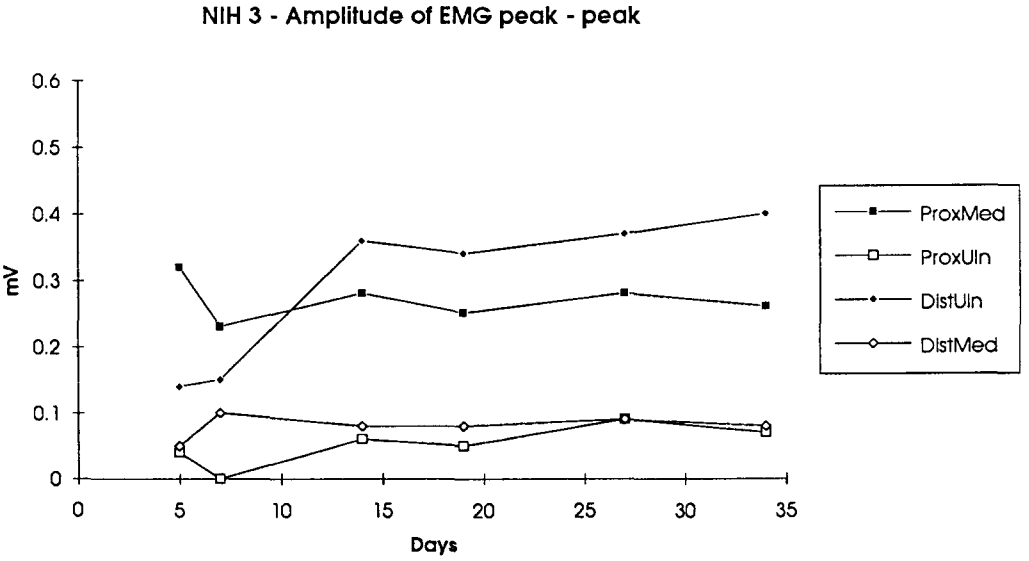

Figure 10

Forelimb task paradigm and development

The purpose of the forelimb task that we are developing is to record the movements and forces generated by the experimental animal as he reaches and manipulates the joystick with the left forepaw. The joystick will also be able to generate perturbations so that the elicited reflex and voluntary responses can be studied.

Forelimb task equipment: Three methods for implementing a joystick with 2 degrees of freedom that are being evaluated and are shown schematically in Fig. 11. The first method is using a 4 bar linkage or the variation of a rotor and connecting rod. The second method is to use two slotted semi circles mounted at 90 degrees to one another. This method is commonly used in joysticks used as input devices e.g. radio control. This method was also used in unpublished work by Alain Berthoz at Laboratoire de Physiologie Neurosensorielle du CNRS in Paris. The third method is described in a Ph.D. thesis in mechanical engineering by Bernard Dov Adelstein from MIT (currently working at NASA AMES). The considerations for us are: cost of implementation, attainable accuracy and performance of the finished product, and ease of computing the transformation from physical distance to motor coordinates.

Software from a similar one-dimensional control system already available in our laboratory is being modified to control the joystick.

A feeding system to deliver a reward is being constructed and it is a modification of the system used by Dr. Kris Horn at the Barrow Neurological Institute in Phoenix, Arizona.

A passive joystick has been constructed and is being used to train the experimental animals.

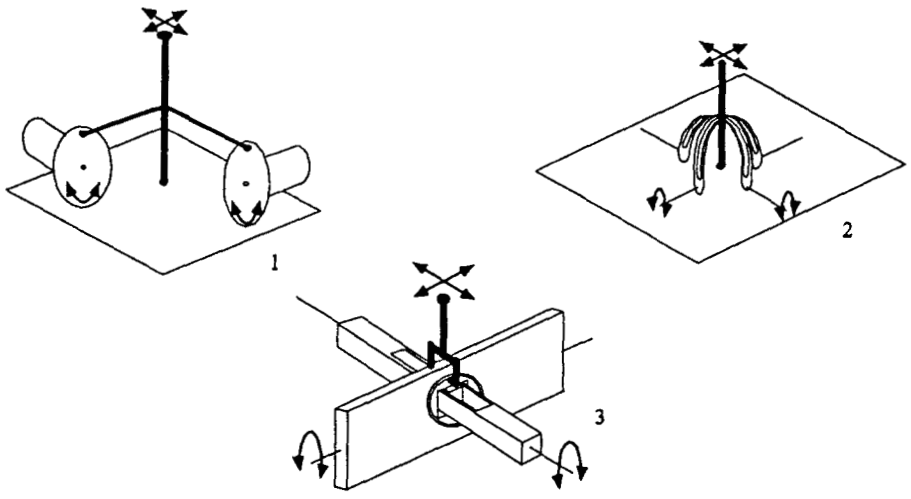

Figure 12

F. Collaborations with Subcontractors

In the second quarter, our collaborations with the two subcontractors for this project, Dr. Dejan Popovic from U. Miami/U. Alberta, and Dr. Jerry Loeb from Queen's U., mainly focused on the analysis and bench testing of the mechanical properties of self-spiraling electrodes that were provided by Dr. Loeb. This study resulted in the identification of several important limitations: difficult and unreliable cuff opening, improper adhesion of the silicone to the polyimide, undesirable separation between the electrodes and the nerve because of the silicone sheet width, unsatisfactory method for opening of windows through silicone to reveal the electrodes, improper sealing after closing, and insufficient robustness of the electrode. A new design which included a new approach to construct these electrodes was formulated by Dr. Hoffer, tested in preliminary version by Drs. Hoffer and Popovic during the latter's visit to SFU on May 10-13, 1993, and communicated to Dr. Loeb subsequently. In essence, the suggested solution entails reversing the layers of polyimide and silicone, by placing the polyimide as the innermost layer and providing a self-coiling double layer of silicone on the outside. This approach is likely to remedy the severe difficulties encountered with the previous version. Dr. Loeb provides a cogent and expanded summary of this new approach in his Progress Report, which is attached to this one.

G. Plans for Next Quarter

In the third quarter we intend to:

1. Complete the implantation of a total of 8 cats that comprise the series for Year 1 of this study.
2. Continue monitoring the status of implanted nerves and electrodes for at least 6 months per cat.
3. Complete the forelimb reaching task paradigm.
4. Complete the design of, and start the construction of hardware for, the reaching task.
5. Train cats on the new forelimb reaching task and start recording data during this task.
6. Collaborate on the bench evaluation of self-spiralling electrodes according to the new design.

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QPR on Nerve Cuff Electrodes

Work at Queen's University, G.E. Loeb, P.I.

Summary

We have worked on gaining experience with fabrication and chronic implantation of nerve cuff electrodes, making incremental modifications of designs to improve surgical handling, biocompatibility and mechanical robustness. We are just starting to work with polyesterimide as a substitute for the polyimide that has been used to date. A new substrate pattern has been designed that will, among other things, take advantage of a novel approach to self-spiralling. This should result in higher yields and simpler, more robust fabrication, particularly of the very small tripolar electrodes required for recording localized sensory information from small cutaneous nerves.

Fabrication

Table 1 - Nerve Cuff Inventory provides an enumeration of the substrates received from Carleton University under our subcontract with them and their disposition in various experiments. Table 2 - Fabrication Steps describes the materials and protocols used.

One of the key materials is thin Silastic sheet. The standard material from Dow Corning (0.005" thick unreinforced) is no longer available and was, in any event, somewhat too thick. We have acquired a press and have been successfully casting our own 0.003" thick sheets using MDX-4210 elastomer.

The process described here includes critical and tedious steps for hand-cutting windows for the contacts through the silicone rubber sheet and applying the contact adhesive to the surface of the polyimide substrate without covering the contacts or the tab region or missing the edges. These problems will be eliminated in the revised approach described below.

The process described here shows only one of the two polyimide tabs in use to open the cuff during implantation. The other edge is opened by a suture loop to overcome the problem noted below of having a polyimide edge inside the cuff.

The cuffs to date have used solder connections for the stainless steel flexible wires (Cooner AS-631), which have been reliable and remained bright under a coating of Silastic Medical Adhesive A. However, this is not an acceptable form of connection for long term implants. We have been formulating platinum-flake filled Medical Adhesive A and testing it for electrical conductivity, mechanical robustness and long term corrosion resistance when used to connect stainless steel wires to the platinum contact pads of the nerve cuffs. When filled to the point of providing good electrical continuity, the material tends to be somewhat friable but very stable and free from corrosion during prolonged saline immersion (now over two months in vitro). When over-coated with unfilled Silastic as insulation and mechanical reinforcement, this material appears promising for long term termination to virtually any inert metal.

Experience with Chronic Animal Implants

The gross and histological appearance of the tissue surrounding nerve cuffs and the polyimide connecting cable and solder pads generally suggest that polyimide is not toxic but it may be mechanically traumatic to adjacent tissue if its sharp, hard edges come into contact with soft tissue. This problem led us to make several minor design modifications in various of the chronic implants to date, including extending the silicone layer past the edges of the polyimide substrate at the ends and open edges of the cuff and laminating the solder pads on a layer on Dacron reinforced Silastic sheet that was also used to carry epimysial patch electrodes for concurrent measurement of EMG.

The chronic experiments also revealed a problem with poor sealing of the polyimide edges to achieve closure. The recorded cutaneous activity from the superficial peroneal and sural nerves and even

from the whole sciatic was quite strong and easily detected in a quiet animal, but considerable EMG interference was noted when the animal was walking around. This interference tended to increase over time and seemed to be correlated with the degree to which a bridge of connective tissue had grown between the nerve in the cuff and the outside tissue. In one extreme case, this bridge had become thick and actually pulled the nerve partially outside the cuff lumen, apparently in response to mechanical trauma from the exposed fold in the polyimide tab.

The cuffs themselves were generally in good condition after 1-2 weeks, with the platinum contacts still bright and tightly adherent in both recording and stimulating cuffs. However, electrical continuity was lost abruptly in three cuffs, apparently from fracture of the polyimide flex lead at the point of narrowing at either the solder pad or the nerve cuff end. The circumstances and microscopic appearance of the fractured ends suggest that they were not ruptured from excessive tensile stress, but rather fractured either spontaneously or as a result of repeated flexion, which would tend to concentrate at the neck regions. This may point to a mechanically accelerated form of the well-known tendency of polyimide to hydrolyze and lose mechanical integrity with prolonged exposure to water.

Experience with Polyesterimide

In anticipation of the fracture problem noted above, the Carleton group has been developing procedures for forming thin-film substrates from polyesterimide, a material that is reputedly more stable in water. This has turned out to require considerable experimentation with toxic solvents and complex cure and etching cycles. So far, this material seems both more prone to fracture and to loss of adhesion, as noted in the test results appended. However, there are still many process variables to be optimized, as was required for polyimide.

New Substrate Design and Rationale

The groups at Simon Fraser and Edmonton have identified a promising new strategy to separate the self-spiralling property from the mechanics of the polyimide substrate by making a self-spiralling laminate of two layers of silicone rubber and rolling the polyimide substrate inside. This substantially simplifies fabrication by eliminating the need to cut holes in the silicone layer to reach the pads and to achieve critical adhesion to pull (rather than push) the relatively stiff substrate material into spiral form. It also makes it easier to extend the silicone layer past all of the polyimide edges and to carry the silicone lamination along the flex-lead portion to reduce the problem of flexion fractures. It also allows us to improve the yield of substrates per wafer by creating a one-size fits all pattern, as shown in Figure 3, and packing them closer on the 4 inch silicon substrate during photolithographic fabrication. The new pattern has five leads in the length previously occupied by three, making it possible to build tripolar electrodes that are half as long and multipolar electrodes for conduction velocity studies. The contacts are also longer and can be trimmed to any desired length so that the same substrate can be rolled into cuffs of any diameter. Both handling tabs have been eliminated because they occupy valuable substrate area and, in the new design, their folded edges would have to be exposed on the closing edges of the spiral. Instead, we will embed handling suture loops either between the two layers of the silicone laminate or between the polyimide and silicone layers.

Plans for Next Quarter

We will continue to develop polyesterimide as a replacement for polyimide. Artwork for the new substrate design will be turned into masks and new cuff substrates will be prepared and integrated with the new fabrication procedures for the revised nerve cuffs. Some of these cuffs will be supplied for acute and chronic experiments at Queen's and Simon Fraser. Based on these results, the incremental design process will undoubtedly continue.

NERVE CUFF INVENTORY June 7, 1993

RECEIVED FROM CARLETON:

MARCH 1	5	POLYESTERIMIDE ELECTRODES
MARCH 30	22	POLYIMIDE ELECTRODES
APRIL 28	15	" "
MAY 27	16	" "
JUNE 8	11	" "

FABRICATED WITH PRE-STRETCHED SILASTIC SHEETING

6	SMALL	POLYIMIDE ELECTRODES
18	MEDIUM	" "
12	LARGE	" "

PREPARED AND STERILIZED FOR IMPLANTATION

12	MEDIUM	POLYIMIDE ELECTRODES
6	LARGE	" "

IMPLANTED IN CATS

6	MEDIUM
3	LARGE

USED FOR OTHER TESTS AND DEMONSTRATIONS

6	SMALL
6	MEDIUM
6	LARGE

Table 2

Fabrication Steps

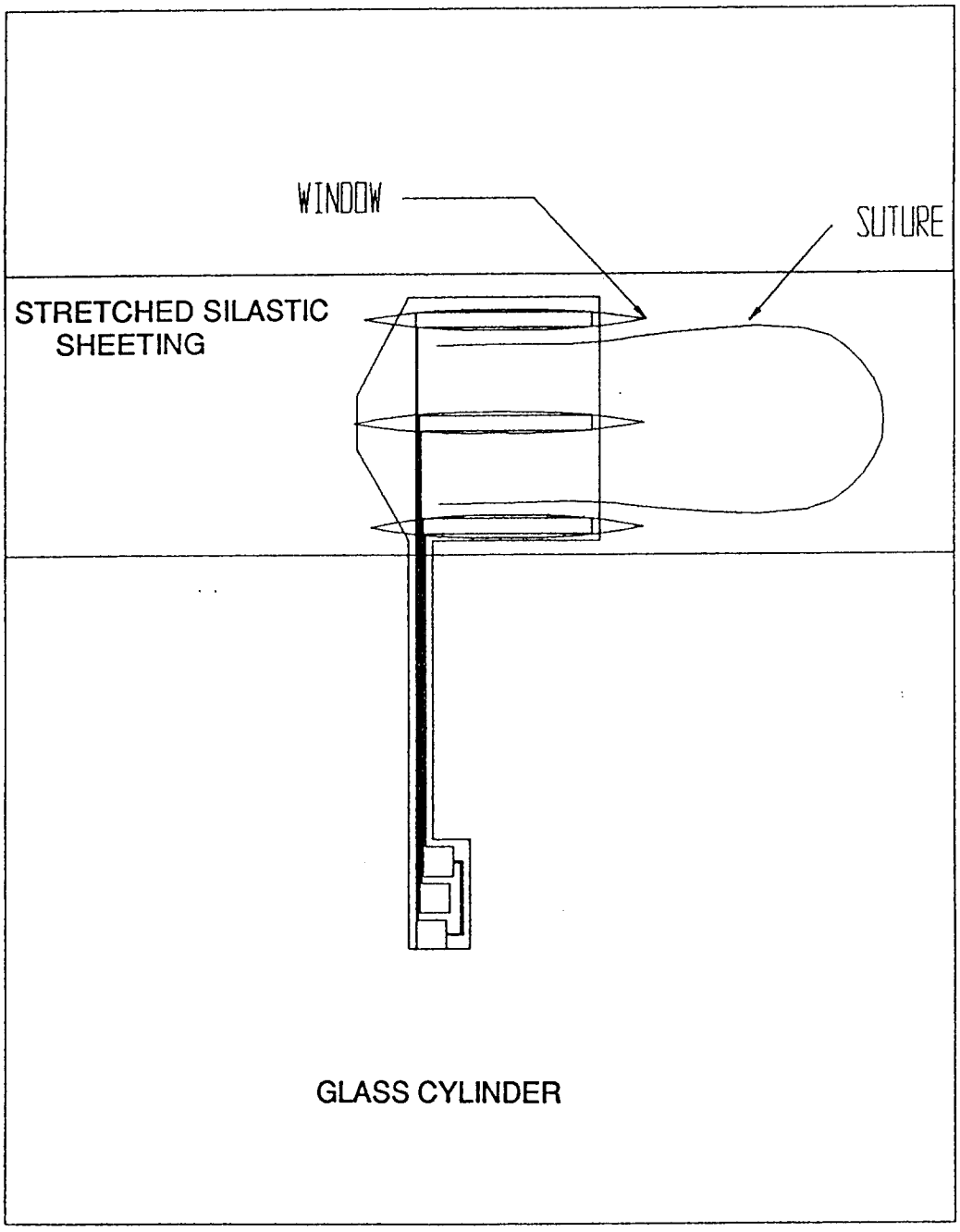
Self-curling Nerve Cuff Electrodes

Step 1.	Mix PSA 529 GE Silicone Adhesive with SRC18 catalyst and 30% toluene as thinning agent.
Step 2.	With polyimide substrate taped flat to glass slide (platinum electrode facing up):
	Paint a smooth, continuous layer of adhesive onto bonding area with 1-0 or 2-0 artist's brush.
Step 3.	Use a 3" diameter glass cylinder (flask or other suitable containers will substitute) and attach photocopy images (actual size) in a row to the inside of the cylinder facing out. These should be well aligned as to form a straight evenly spaced band around the inside of the cylinder.
Step 4.	Pre form a sheet of silastic by compressing and curing MDX 4210 between two sheets of plate glass in a press (.003" thick). Cut out a band of pre determined width (depending on the size of the cuff).
Step 5.	The band of silastic sheeting is now stretched around the glass cylinder (using a pre determined amount of force) being careful to follow the boundaries of the nerve cuff images on the inside of the glass cylinder. [Note the sheeting must be well cleaned in water].
Step 6.	Paint a smooth continuous layer of PSA 529 over the image area (as seen through the clear sheeting and glass to the image area taped to the inside of the cylinder).
Step 7.	Using a fresh #11 scalpel, cut windows into the silastic sheeting which correspond to the rectangular electrode areas. (As seen through glass). Figure 1
Step 8.	Attach a loop of 6-0 suture (woven) to the layer of adhesive on the silastic. Figure 1
Step 9.	Carefully place the electrode on to the silastic so that the two surfaces of adhesives come together. Alignment is achieved visually suing the electrode image as seen through the glass.
Step 10.	Using a rounded smooth metal instrument press the two surfaces together (most air spaces will be eliminated during this process indicating a good bond). Figure 2
Step 11.	Fold tab and crease polyimide.
Step 12.	Following a 24 hour cure at room temperature, cuff can be removed by cutting around the perimeter with a scalpel and carefully lifting the cuff.

SELF CURLING NERVE CUFF FABRICATION

APRIL 2, 1993

Fig. 1



SELF CURLING NERVE CUFF FABRICATION

April, 2, 1993

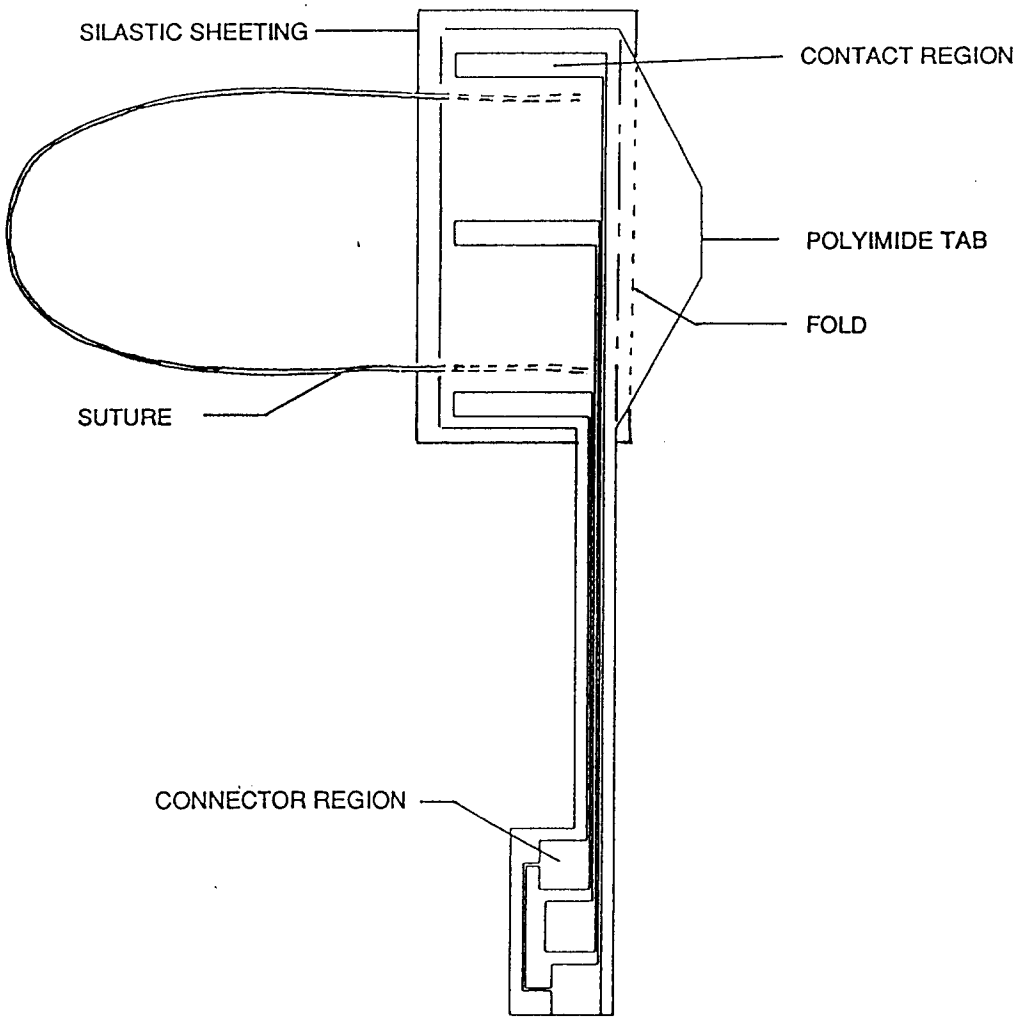
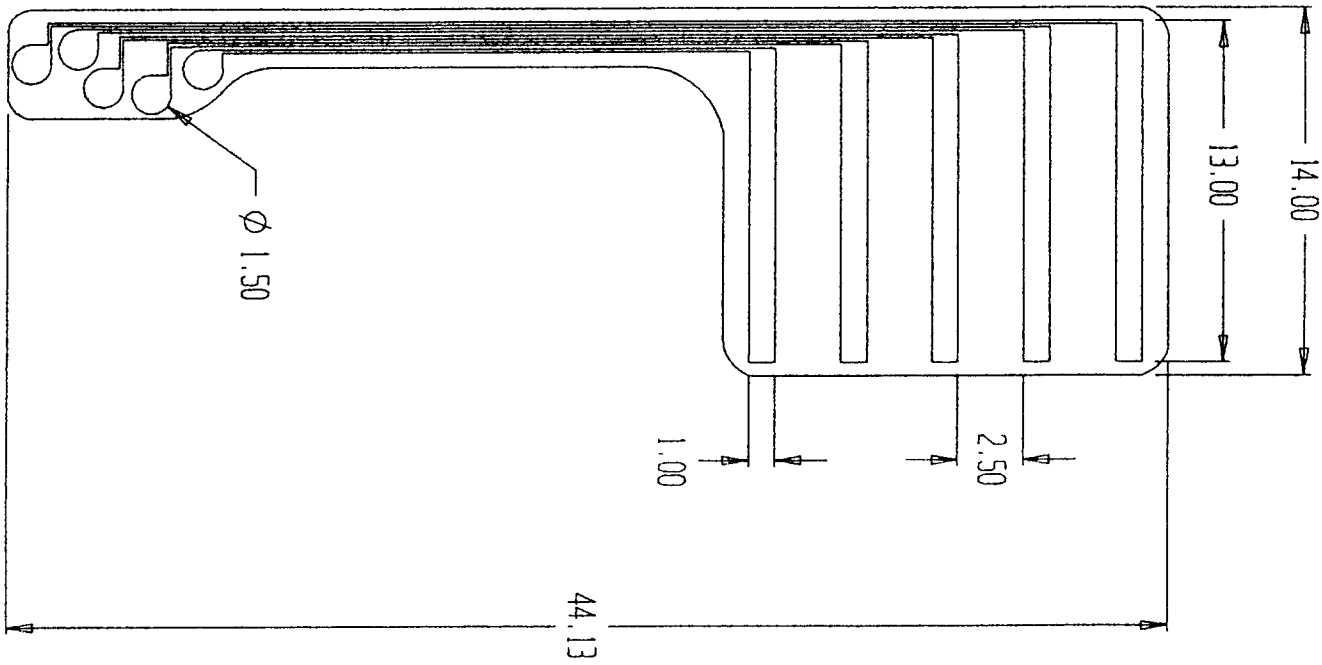


Fig. 2

Figure 3. The new design for the self spiraling nerve cuff electrode as discussed at the special projects meeting is as follows:

1. The overall length of the contact region (electrode) will be increased by approximately 1 mm.
2. All corners on substrate will include a radius to eliminate points that could damage tissue.
3. Connector areas (solder pads) will be smaller
4. A one size fits all concept will include the addition of two more contact areas.
5. Silastic sheeting will be laminated prior to adhesion to substrate (laminate two sheets, one sstretched and one relaxed). Pre stressed laminated sheet is then glued to electrode substrate on the opposite side of exposed contact region (Pf electrode). It may be sufficient and perhaps desirable to glue the substrate to the silicone at only one longitudinal band so that it can creep with respect to the silicone when it curls into a spiral.



MODIFIED DESIGN
NERVE CUFF ELECTRODE
JUNE 1 / 1993

Fig. 3

Appendix

Tests on Polyesterimide Electrode Substrates

A large cuff electrode was fitted with stranded stainless steel leads soldered to the connector pads and covered with Medical Adhesive "A".

The impedence was measured (after bubble testing) at 4 K ohms.

The electrodes was stimulated in saline for 24 hrs. using a cycle of 20 ms (50 pps), a current of 1 mA and a pulse width of 50 μs.

The impedence was again measured and was .5 K ohms after 24 hrs.

The electrode was put back on test for another 24 hrs. of stimulation. Impedence was then tested and remained unchanged.

The electrode was inspected visually and found to have separation of the electrodes from the substrate. Although still intact, the Pt layer was completely separated from the polyesterimide and could be easily removed.

Previous visual inspection (prior to tests) of this electrode revealed small ripples in the platinum layer and adhesion appeared to be marginal.

May 24, 1993
Dejan Popović, Professor

II QUARTERLY REPORT - February, 16 1993.- May, 16, 1993.

Research Contract #NO1-NS-3-2380 NINDS, Washington, D.C.

The following has been accomplished at the University of Miami, Miami, Florida:

1) Dr Dejan Popović participated in cat experiments at the SFU, B.C. (4 days) and spent two days with Dr Stein at the University of Alberta discussing possible direction in improvements of the design of electrodes.

2) D.Popović gave a presentation about recent achievements and problems in the field of functional electrical stimulation to the staff of Dr Hoffer's Lab.

3) Mr Zoran Nikolić continued with recordings from chronic cat preparations (hind limb) at the University of Miami (funded by The Miami Project to Cure Paralysis) to learn more about the neural recordings with cuff electrodes. The attention was paid on how to optimize the portable signal processing unit. At this time he is concentrated on analog hard-wired circuitry for processing and simple pattern recognition techniques, such as threshold detection or ramp detection.

4) Mr. Zoran Nikolić, helped by Drs. Popović is finishing the improved, portable, battery operated, low-noise device that will allow recording from peripheral nerves diminishing most of the EMG contamination and stimulation artifacts. This work is under testings in chronic cats at the University of Miami (funded by The Miami Project to Cure Paralysis), and the paper titled "Low Noise Gated Amplifier for Neural and Muscular Recordings in FES Systems" by Z. Nikolić, D. Popović, R.B. Stein and Z. Kenwell was submitted to IEEE Trans. on Biomedical Engineering in March, 1993. Part of this research was funded by this contract.

Research plan for the coming period, (Quarter 3, Year 1)

1) We will continue the development of the amplifier and processing circuit for neural signals, to be used for recordings in freely moving animals.

2) We are expecting to get some recordings from cat experiments at SFU, and start their processing. The plan is that Mr Nikolić spend about 7 to 10 days at SFU and participate in experiments. This stay will allow him to learn about specifics of tests that are under development at SFU. Our recent experience shows that it is extremely important to have a full understanding on motor activities when analyzing signals.

3) Mr Nikolić will continue the development of the use of VideoBlaster hardware and software, by writing additional software, to facilitate the analysis of signals.

4) Dr Popović will concentrate to human studies in evaluating further which nerves should be instrumented with cuff electrodes.